

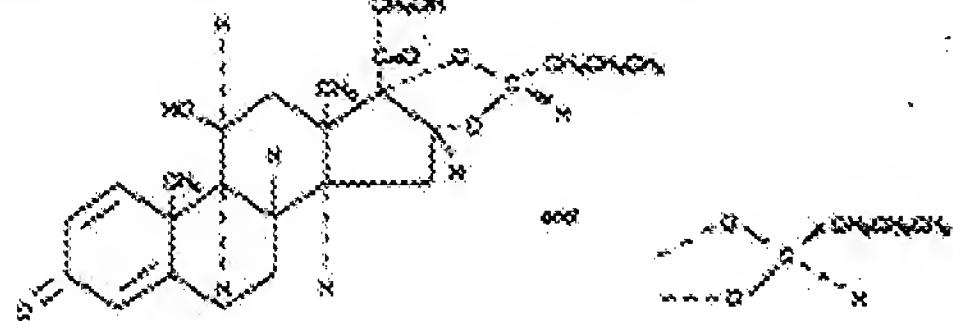
## **EXHIBIT “1”**

# Pulmicort Turbuhaler® 200 mcg (budesonide inhalation powder)

## For Oral Inhalation Only.

### DESCRIPTION

Budesonide, the active component of PULMICORT TURBUHALER 200 mcg, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-tetrahydroxyprogna-1,4-diene-3,20-dione cyclic 18,17-estrol with hydroxymethyl. Budesonide is provided as a mixture of two epimers (22S and 22R). The empirical formula of budesonide is  $C_{22}H_{28}O_9$ , and its molecular weight is 402.5. Its structural formula is:



Budesonide is a white to off-white, colorless powder that is practically insoluble in water and in acetone, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is  $1.8 \times 10^2$ .

PULMICORT TURBUHALER is an inhalation-dry powder inhaler which contains only inhaled budesonide. Each actuation of PULMICORT TURBUHALER provides 200 mcg budesonide per metered dose, which delivers approximately 150 mcg budesonide from the mouthpiece (measured in vitro testing at 60 L/min for 2 sec). The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow (see Patient's Instructions for Use). In adult patients with asthma (mean FEV<sub>1</sub> 2.9 L [0.1 - 5.1 L] mean peak inspiratory flow [PIF] through PULMICORT TURBUHALER was 78 [40-111] L/min. Similar results (mean PIF 32 [43-125] L/min) were obtained in pediatric children (6 to 10 years) mean FEV<sub>1</sub> 2.1 L [0.3 - 5.4 L].

### CLINICAL PHARMACOLOGY

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In contrast to *in vitro* and animal models, budesonide has approximately a 300-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (per micron of oil see *assay* assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered systemically and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid action on inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, leukotrienes, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses from PULMICORT TURBUHALER. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first-pass hepatic degradation of orally absorbed drug (55-95%), and the low potency of formed metabolites (see *table*).

#### Pharmacokinetics

The activity of PULMICORT TURBUHALER is due to the parent drug. Budesonide, in glucocorticoid receptor affinity studies, the 22S form was two times as active as the 22R epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert. The 22S form was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22R-form. The terminal half-life, 2 to 3 hours, was the same for both isomers and was independent of dose. In asthmatic patients, budesonide showed a small increase in AUC and C<sub>max</sub> with increasing dose after both a single dose and repeated dosing from PULMICORT TURBUHALER.

**Absorption:** After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 5-15%. In contrast, most of budesonide delivered to the lungs is systemically absorbed. In healthy subjects, 34% of the inhaled dose was deposited in the lungs (as assessed by plasma concentration method) with an absolute systemic availability of 20% of the inhaled dose. Pharmacokinetics of budesonide do not differ significantly in healthy volunteers and asthmatic patients. Peak plasma concentrations of budesonide occurred within 30 minutes of inhalation from PULMICORT TURBUHALER.

**Distribution:** The volume of distribution of budesonide was approximately 3 L/kg. It was 55-95% bound to plasma protein. Protein binding was constant over the concentration range (1-100 ng/ml) achieved with, and exceeding, recommended doses of PULMICORT TURBUHALER. Budesonide showed little or no binding to corticosteroid-binding globulins. Budesonide rapidly equilibrated with red blood cells in a concentration-independent manner with a blood/plasma ratio of about 0.8.

**Metabolism:** *In vitro* studies with human liver hepatocytes have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 3A catalyzed hydroxylation have been isolated and identified as 16α-hydroxybudesonide and 20-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolite patterns have been detected. Hepatic metabolic inactivation was observed in human lung and serum preparations.

**Excretion:** Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an inavenous radio-labeled dose was recovered in the urine. Unchanged budesonide was detected in the urine.

**Special Population:** No pharmacokinetic differences have been described due to race, gender or advanced age.

**Pediatrics:** Following inhaled dosing in pediatric patients age 10-14 years, plasma half-life was shorter than in adults (1.5 hr vs. 2.0 hr in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

**Hepatic insufficiency:** Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were altered by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The inhaled pharmacokinetics of budesonide were, however, similar in hepatic patients and in healthy subjects.

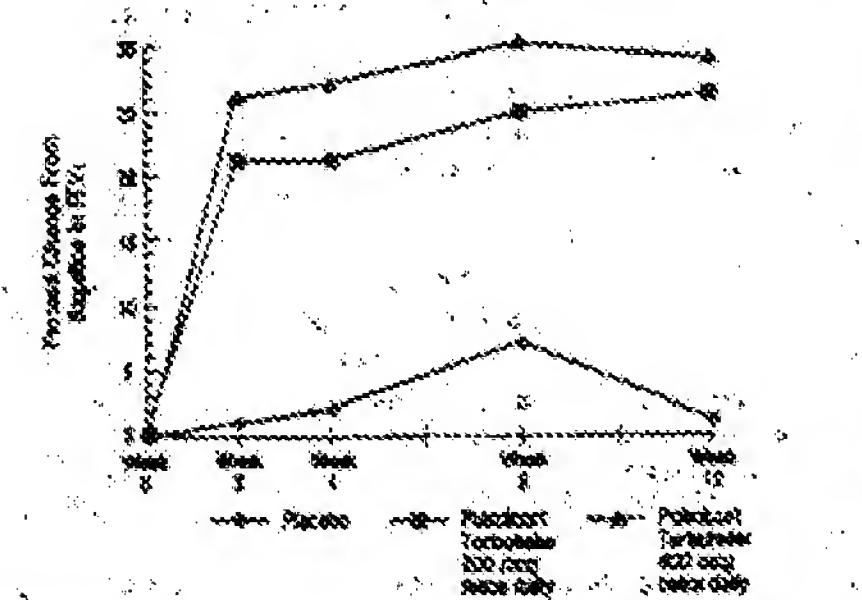
**Drug-drug interactions:** Ketoconazole, a potent inhibitor of cytochrome P450 3A, the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, ketoconazole had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

#### Pharmacodynamics

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered-dose inhaler with a dose spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally ingested budesonide is largely explained by its direct action on the respiratory tract.

Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within

### A 12-Week Trial in Patients Not on Corticosteroid Therapy Prior to Study Entry

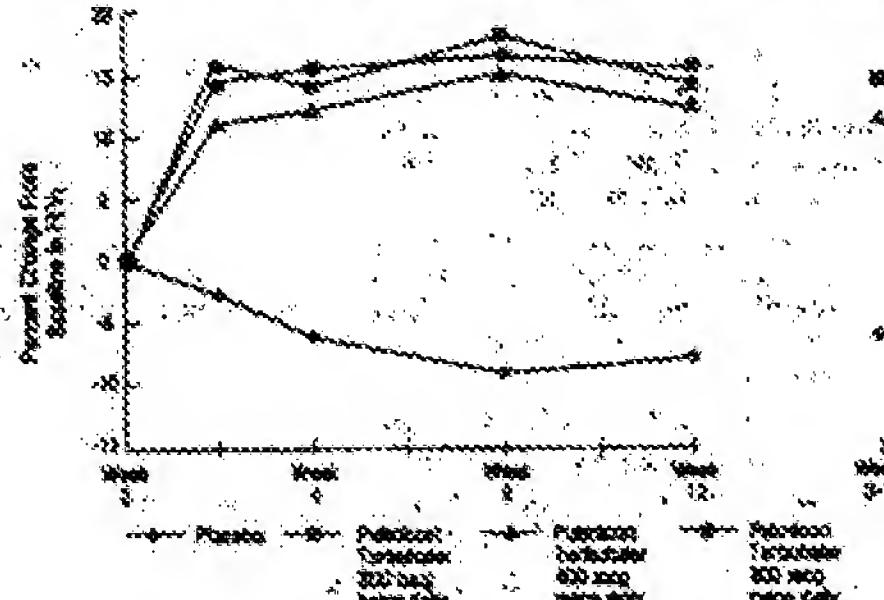


In a 12-month controlled trial in 75 patients not previously receiving corticosteroids, PULMICORT TURBUHALER at 200 mcg twice daily resulted in improved lung function (measured by FEV<sub>1</sub>) and reduced bronchial hyperactivity compared to placebo.

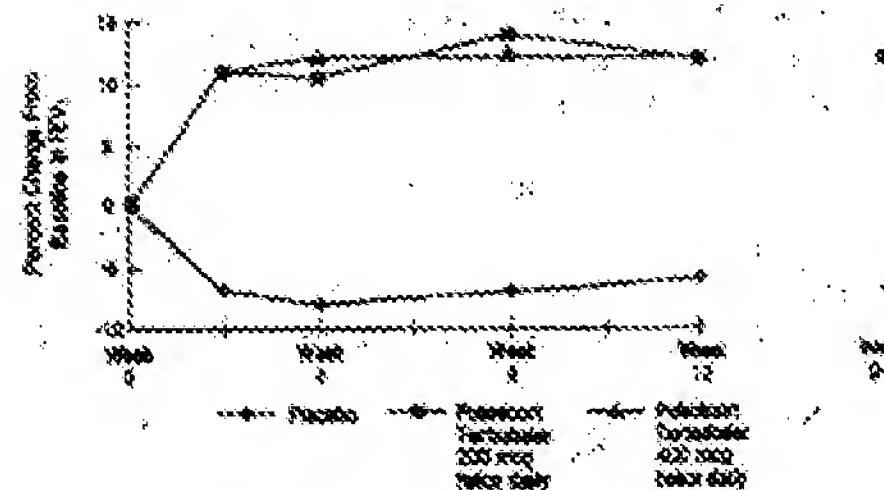
#### Patients Previously Maintained on Inhaled Corticosteroids

The safety and efficacy of PULMICORT TURBUHALER was also evaluated in adult and pediatric patients (age 5 to 18 years) previously maintained on inhaled corticosteroids (adults: N=472, mean baseline FEV<sub>1</sub> 2.04 L, baseline doses of beclomethasone dipropionate 128-1008 mcg/day; pediatric: N=414, mean baseline FEV<sub>1</sub> 2.09 L, baseline doses of beclomethasone dipropionate 129-677 mcg/day or budesonide acetone 300-1800 mcg/day). The FEV<sub>1</sub> results of these two trials, both 12 weeks in duration, are presented in the following figures. Pulmonary function improved significantly with all doses of PULMICORT TURBUHALER compared to placebo in both trials.

#### Adult Patients Previously Maintained on Inhaled Corticosteroids



#### Pediatric Patients Age 6 to 18 Years Previously Maintained on Inhaled Corticosteroids



#### Patients Previously Maintained on Oral Corticosteroids

In a clinical trial in 169 severe asthmatic patients requiring chronic oral prednisone therapy (mean baseline prednisone dose 19.3 mg/day), PULMICORT TURBUHALER at doses of 400 mcg twice daily and 800 mcg twice daily was compared to placebo over a 20-week period. Approximately two-thirds (68% on 400 mcg twice daily and 64% on 800 mcg twice daily) of PULMICORT TURBUHALER-treated patients were able to achieve sustained (at least 2 weeks) oral corticosteroid cessation (compared with 8% of placebo-treated patients) and improved asthma control. The average oral corticosteroid dose was reduced by 83% on 400 mcg twice daily and 79% on 800 mcg twice daily for PULMICORT TURBUHALER-treated patients vs. 23% for placebo. Additionally, 58 out of 64 patients (91%) who completely discontinued oral corticosteroids during the double-blind phase of the trial remained off oral corticosteroids for an additional 12 months while receiving PULMICORT TURBUHALER.

#### INDICATIONS AND USAGE

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

PULMICORT TURBUHALER is NOT indicated for the relief of acute bronchospasm.

#### CONTRAINDICATIONS

PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

PULMICORT TURBUHALER has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, adenosine triphosphate, and adenosine monophosphate in hyperreactive patients. The clinical relevance of these models is not certain.

Treatment with PULMICORT TURBUHALER 300 mcg daily (300 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEF<sub>250</sub> following inhaled antigen challenge. 2,3 The effects of PULMICORT TURBUHALER on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 825 adult and 339 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with PULMICORT TURBUHALER treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 5%, and 10% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg budesonide twice daily via PULMICORT TURBUHALER for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (8-hour ACTH infusion) while 16 mcg prednisone resulted in a 35% reduction. In this study, no patient on PULMICORT TURBUHALER at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1129 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of PULMICORT TURBUHALER when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of PULMICORT TURBUHALER at recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

The administration of budesonide via PULMICORT TURBUHALER at doses up to 800 mcg/day (mean daily dose 445 mcg/day) or via a pressurized metered-dose inhaler in doses up to 1200 mcg/day (mean daily dose 625 mcg/day) in 218 pediatric patients (age 3 to 11 years) for 2 to 5 years had no significant effect on stature growth compared with non-corticosteroid therapy in 82 matched control patients. However, the long-term effect of PULMICORT TURBUHALER on growth is not fully known.

#### CLINICAL TRIALS

The therapeutic efficacy of PULMICORT TURBUHALER has been evaluated in controlled clinical trials involving more than 1000 patients (6 years and older) with asthma of varying disease duration (<1 year to >20 years) and severity.

Double-blind, parallel, placebo-controlled clinical trials of 12 weeks duration and longer have shown that, compared with placebo, PULMICORT TURBUHALER significantly improves lung function (measured by PEF and FEV<sub>1</sub>), significantly decreased nocturnal and daytime symptoms of asthma, and significantly reduced the need for as-needed inhaled  $\beta_2$ -agonist use at doses of 400 mcg to 1600 mcg per day (200 mcg to 800 mcg twice daily) in adults and 400 mcg to 800 mcg per day (200 mcg to 400 mcg twice daily) in pediatric patients 6 years of age and older.

Improved lung function (increasing PEF) was observed within 24 hours of starting treatment in both adult and pediatric patients 6 years of age and older, although maximum benefit was not achieved for 1 to 2 weeks, or longer, after starting treatment. Improved lung function was maintained throughout the 12 weeks of the double-blind portion of the trials.

#### Patients Not Receiving Corticosteroid Therapy

In a 12-week clinical trial in 273 patients with mild to moderate asthma (mean baseline FEV<sub>1</sub> 2.27 L) who were not well controlled by bronchodilator alone, PULMICORT TURBUHALER was evaluated at doses of 200 mcg twice daily and 400 mcg twice daily versus placebo. The FEV<sub>1</sub> results from this trial are shown in the figure below. Pulmonary function improved significantly on both doses of PULMICORT TURBUHALER compared with placebo.

Hypersensitivity to budesonide contraindicates the use of PULMICORT TURBUHALER.

#### WARNING

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER because deaths due to adrenal insufficiency have occurred in pediatric patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawn from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been given completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastrointestinal) or other conditions associated with severe electrolyte loss. Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiologic amounts of glucocorticoids systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (or large doses) immediately and to contact their physician for further instructions. These patients should also be instructed to carry a medical identification card indicating that they may need supplemental systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT TURBUHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, and eczema (see Dosage and Administration).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressive doses of corticosteroids. In pediatric or adult patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IMIG) may be indicated. (See the respective package insert for complete VZIG and IMIG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an increased increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with PULMICORT TURBUHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT TURBUHALER should be discontinued and alternate therapy initiated.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT TURBUHALER. During such episodes, patients may require therapy with oral corticosteroids.

#### PRECAUTIONS

**General:** During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, headache, and depression, despite readministration or even discontinuation of respiratory therapy.

## Patient's Instructions for Use

### Pulmicort<sup>®</sup> Turbuhaler<sup>™</sup> (budesonide inhalation powder)

Pulmicort Turbuhaler<sup>™</sup> 200 mcg  
(budesonide inhalation powder)



#### WHAT YOU SHOULD KNOW ABOUT PULMICORT TURBUHALER<sup>™</sup>

Your doctor has prescribed Pulmicort Turbuhaler 200 mcg. It contains a medication called budesonide, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

Pulmicort Turbuhaler treats the inflammation—the “quiet part” of asthma that you cannot hear, see, or feel. When inflammation is left untreated, your asthma symptoms and attacks can increase. Pulmicort Turbuhaler works to prevent and reduce your asthma symptoms and attacks.

#### IMPORTANT POINTS TO REMEMBER ABOUT PULMICORT TURBUHALER<sup>™</sup>

- 1. **MAKES SURE** that this medicine is suitable for you (see “BEFORE USING YOUR PULMICORT TURBUHALER” below).
- 2. It is important that you inhale each dose as your doctor has advised.
- 3. Use your Turbuhaler as directed by your doctor. **DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU FEEL BETTER**, unless told to do so by your doctor.

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine.

FOR FURTHER INFORMATION ASK YOUR DOCTOR OR PHARMACIST.

**DO NOT** inhale more doses or use your Turbuhaler more often than instructed by your doctor.

**This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack.** It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.

**Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:**

**an asthma attack does not respond to the additional medication,**

**you require more of the additional medication than usual.**

**If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using your Pulmicort Turbuhaler.**

#### BEFORE USING YOUR PULMICORT TURBUHALER

#### TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:

- 1. If you are pregnant (or intending to become pregnant).
- 2. If you are breast-feeding a baby.
- 3. If you are allergic to budesonide or any other orally inhaled corticosteroid.

In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

#### USING YOUR PULMICORT TURBUHALER

**Follow the instructions shown on the other side. If you have any problems, tell your doctor or pharmacist.**

**It is important that you inhale each dose as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.**

#### DOSE

**Use as directed by your doctor.**

**It is VERY IMPORTANT that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler.**

**DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.

**I may take 1 to 2 weeks or longer before you feel maximum improvement, so IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER, unless told to do so by your doctor.**

**If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.**

PULMOCORT TURBULEHALER will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since inhaled corticosteroids are absorbed into the circulation 20% to 30% systemically above therapeutic doses, the less beneficial effects of PULMOCORT TURBULEHALER in minimizing HPA dysfunction may be expected over other recommended doses. Inhaled and inhaled corticosteroids are treated to the lowest effective dose, given individual propensity to effects on cortisol production levels, physicians should consider this information when prescribing PULMOCORT TURBULEHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of hirsutism, adrenal response.

It is possible that systemic corticosteroid effects such as hypertension and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMOCORT TURBULEHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

Although patients in clinical trials have received PULMOCORT TURBULEHALER on a continuous basis for periods of 1 to 2 years, the long-term local and systemic effects of PULMOCORT TURBULEHALER in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMOCORT TURBULEHALER on developmental or immunological processes in the mouth, pharynx, trachea and lung are unknown.

In clinical trials with PULMOCORT TURBULEHALER, localized infections with fungal colonies occurred in the mouth and pharynx in some patients. If respiratory-tract candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with PULMOCORT TURBULEHALER therapy, but if fungal therapy with PULMOCORT TURBULEHALER may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis, infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

Rare instances of glaucoma, increased intracranial pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

**Information for Patients:** For proper use of PULMOCORT TURBULEHALER and to obtain maximum improvement, the patient should read and follow the accompanying Patient's instructions for the inhaler. In addition, patients being treated with PULMOCORT TURBULEHALER should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a substitute of all possible adverse or intended effects.

Patients should take the medication as directed and use PULMOCORT TURBULEHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.

• PULMOCORT TURBULEHALER is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.

• PULMOCORT TURBULEHALER must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose. PULMOCORT TURBULEHALER must be primed when the unit is used for the very first time. To prime the unit, hold the unit in an upright position and turn the brown grip fully to the right, then fully to the left and 8 clicks. Repeat. The unit is now primed and ready to load the first dose by turning the grip fully to the right and fully to the left until 8 clicks.

On subsequent uses, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use. Turn the brown grip fully to the right, then fully to the left and 8 clicks. During inhalation, PULMOCORT TURBULEHALER must be held in the upright (mouthpiece up) or horizontal position. Do not shake the inhaler. Place the mouthpiece between lips and inhale forcefully and deeply. The powder is then delivered to the lungs.

• Patients should not exhale through PULMOCORT TURBULEHALER.

• Due to the small volume of powder, the patient may not taste or sense the presence of any medication entering the lungs when inhaling from TURBULEHALER. This lack of "sensation" does not indicate that the patient is not receiving benefit from PULMOCORT TURBULEHALER.

• Rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.

• When there are 20 doses remaining in PULMOCORT TURBULEHALER, a red mark will appear in the indicator window.

• PULMOCORT TURBULEHALER should not be used with a spacer.

• The mouthpiece should not be broken or chewed.

• The cover should be replaced securely after each use.

• Keep PULMOCORT TURBULEHALER clean and dry at all times.

• Improvement in asthma control following inhalation of PULMOCORT TURBULEHALER can occur within 24 hours of beginning treatment although benefit may not be achieved for 1 to 2 weeks, or longer if symptoms do not improve in this time frame, or if the condition worsens, the patient should be instructed to contact the physician.

• Patients should be warned to avoid exposure to chicken pox or shingles and if they are exposed, to contact their physician without delay.

• For proper use of PULMOCORT TURBULEHALER and to obtain maximum improvement, the patient should read and follow the accompanying Patient's instructions for use.

**Drug Interactions:** In clinical studies, concurrent administration of beclomethasone and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. Beclomethasone, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of beclomethasone during concurrent dosing. The clinical significance of concurrent administration of beclomethasone with PULMOCORT TURBULEHALER is not known, but caution may be warranted.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of beclomethasone.

There was no evidence of a carcinogenic effect when beclomethasone was administered orally for 101 weeks to mice at doses up to 200 mcg/kg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis).

In a 104-week carcinogenicity study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving oral doses of 50 mcg/kg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis) or male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in beclomethasone-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and fluticasone scopolide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three treated groups

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1,118 adult and pediatric patients age 6-70 years (472 females and 646 males) were treated with PULMOCORT TURBULEHALER (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

The following table shows the incidence of adverse events in patients previously receiving inhaled corticosteroids and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years), and 332 male and 331 female adult patients (age 18 years and greater).

Adverse Event	Adverse Events with a 2% incidence reported by patients on PULMOCORT TURBULEHALER		
	Placebo N=324 %	200 mcg twice daily N=388 %	800 mcg twice daily N=382 %
<b>Respiratory System</b>			
Respiratory infection	17	20	24
Pharyngitis	5	10	8
Soreness	7	11	7
Voice alteration	0	1	2
<b>Body As A Whole</b>			
Headache	7	14	13
Flu syndrome	6	6	5
Pain	2	5	5
Back pain	1	2	0
Fever	2	2	0
<b>Digestive System</b>			
Oral candidiasis	2	0	4
Dyspepsia	2	1	2
Gastroenteritis	1	1	2
Nausea	2	2	3
<b>Average Duration of Exposure (days)</b>	99	78	80

The table above includes all events (whether considered drug-related or not drug-related by the investigator) that occurred at a rate of 2% or more in any one PULMOCORT TURBULEHALER group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for PULMOCORT TURBULEHALER patients should be taken into account.

The following other adverse events occurred in these clinical trials using PULMOCORT TURBULEHALER with an incidence of 1 to 2% and were more common on PULMOCORT TURBULEHALER than on placebo.

**Body As A Whole:** back pain

**Cardiovascular:** syncope

**Digestive:** abdominal pain, dry mouth, vomiting

**Metabolic and Nutritional:** weight gain

**Musculoskeletal:** fracture, myopathy

**Neurologic:** hypertension, hypotension

**Respiratory:** bleeding, coughing, respiratory tract infection

**Respiratory Mechanistic:** infection

**Special Senses:** taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of PULMOCORT TURBULEHALER 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or not drug-related by the investigator, reported in more than five patients in the PULMOCORT TURBULEHALER group and which occurred more frequently with PULMOCORT TURBULEHALER than placebo are shown below (% PULMOCORT TURBULEHALER and % placebo). In considering these data, the increased average duration of exposure for PULMOCORT TURBULEHALER patients (73 days for PULMOCORT TURBULEHALER vs 41 days for placebo) should be taken into account.

**Body As A Whole:** headache (17% and 2%)

headache (12% and 2%)

pain (10% and 2%)

**Digestive:** dyspepsia (8% and 0%)

nausea (5% and 0%)

oral candidiasis (1% and 0%)

**Musculoskeletal:** arthralgia (0% and 0%)

**Respiratory:** cough increased (6% and 2%)

respiratory infection (32% and 13%)

nausea (1% and 0%)

headache (1% and 0%)

**Pediatric Studies:** In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 16 years) was comparable for PULMOCORT TURBULEHALER (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events by children compared with those reported in adults.

**Adverse Event Reports From Other Sources:** Rare adverse events reported in the published literature or from marketing experience include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; syncoptic or hypotension and hypertension; psychiatric symptoms including depression, agitated reactions, irritability, anxiety and psychosis.

**OVERDOSAGE:**

The potential for acute toxic effects following overdose of PULMOCORT TURBULEHALER is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypertension may occur (see PRECAUTIONS). Administration of 100 mcg twice daily for 8 weeks caused a significant reduction (27%) in the plasma cortisol response to a 50-mg infusion of ACTH compared with placebo (-1%). The corresponding effect of 10 mcg prednisone daily was a 25% reduction in the plasma cortisol response to ACTH.

The minimal lethal oral dose in mice was 100 mg/kg (approximately 200 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). There were no deaths following the administration of an inhalation dose of 60 mg/kg in rats (approximately 360 times the maximum recommended human daily inhalation dose on a mcg/m<sup>2</sup> basis). The minimal oral lethal dose was 200 mg/kg in mice and less than 100 mg/kg in rats (approximately 500 times the maximum recommended human daily inhalation dose based on a mcg/m<sup>2</sup> basis).

**DOSEAGE AND ADMINISTRATION:**

PULMOCORT TURBULEHALER should be administered by the orally inhaled route in asthmatic patients age 6 years and older. Inhaled patients will experience a variable onset and degree of symptom relief. Generally, PULMOCORT TURBULEHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of PULMOCORT TURBULEHALER can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks, or longer. The safety and efficacy of PULMOCORT TURBULEHALER when administered in excess of recommended doses has not been established.

prednisone, prednisolone, triamcinolone acetonide) in these studies.

The mutagenic potential of budesonide was evaluated in six different test systems: Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, cell-linked repressor linked test in Chinese hamster, and DNA repair analysis in rat hepatocyte culture. Budesonide was not mutagenic or clastogenic in any of these tests.

The effect of subcutaneous budesonide on fertility and general reproductive performance was studied in rats. At 20 mcg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mg/mg basis), decrease in maternal body weight gain, percent viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mg/mg basis).

**Pregnancy:** **Teratogenic Effects:** Pregnancy Category C. As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at subcutaneous doses of 20 mcg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mg/mg basis) in rabbits and 200 mcg/day (approximately 2 1/2 times the maximum recommended human daily inhalation dose on a mg/mg basis) in rats.

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by injection at doses of 100 to 250 mcg/day (approximately 1/4 to 1/2 times the maximum recommended human daily inhalation dose on a mg/mg basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic doses appeared to indicate that infants are more prone to teratogenic effects from corticosteroids than humans.

**Non-teratogenic Effects:** Hypothalamic-pituitary-adrenal axis suppression may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

**Nursing Mothers:** Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

**Pediatric Use:** Safety and effectiveness of PULMICORT TURBUHALER in pediatric patients below 5 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with PULMICORT TURBUHALER was similar between the 6- to 10-year age group (N=272) compared with the 10- to 17-year age group (N=134).

Oral corticosteroids have been shown to cause growth suppression in pediatric and adolescent patients, particularly with higher doses over extended periods. If a pediatric or adolescent patient on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to the effect of corticosteroids should be considered (see PRECAUTIONS).

**Geriatric Use:** One hundred patients 65 years or older were included in the US and non-US controlled clinical trials of PULMICORT TURBUHALER. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

#### ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT TURBUHALER:

**ASTRA** Astra USA, Inc., Worcester, MA 01651

#### HOW TO USE YOUR PULMICORT TURBUHALER

Read the complete instructions carefully and use only as directed.

#### BEFORE YOU USE A NEW PULMICORT TURBUHALER

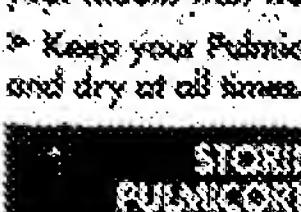
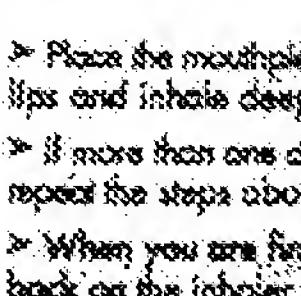
Before you use a new Pulmicort Turbuhaler for the first time, you should prime it. To do this, turn the cover and tilt off. Hold Pulmicort Turbuhaler upright (with mouthpiece up), then twist the brown grip fully to the right and back again to the left. Repeat. Now you are ready to use it. You do not have to prime it any other time after this, even if you put it aside for a prolonged period of time.

#### FOLLOW THE INSTRUCTIONS BELOW.

#### 1. LOADING A DOSE

- Twist the cover and tilt off.
- In order to provide the correct dose, Pulmicort Turbuhaler must be held in the upright position (mouthpiece up) whenever a dose of medication is being loaded.

- Twist the brown grip fully to the right as far as it will go. Twist it back again fully to the left.



#### STORING YOUR PULMICORT TURBUHALER

- After each use, place the white cover back on and twist it firmly into place.
- Keep Pulmicort Turbuhaler in a dry place of controlled room temperature, 68° to 77°F (20° to 25°C).

The recommended starting dose and the highest recommended dose of PULMICORT TURBUHALER, based on prior asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults	Bronchodilator alone	200 to 400 mcg twice daily
	Inhaled Corticosteroid	200 to 400 mcg twice daily
	Oral Corticosteroid	400 to 800 mcg twice daily
Children	Bronchodilator alone	200 mcg twice daily
	Inhaled Corticosteroid	200 mcg twice daily
	Oral Corticosteroid	The highest recommended dose in children is 400 mcg twice daily

#### Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT TURBUHALER should be used concurrently with the patient's usual maintenance dose of systemic corticosteroids. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. The next reduction is made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for adverse toxicity, including objective measures of steroid function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g. joint and/or muscular pain, fatigue and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT TURBUHALER but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawn should commence more slowly. During periods of stress or a severe asthma attack, these patients may require supplemental treatment with systemic corticosteroids.

NOTE: In all patients it is desirable to switch to the lowest effective dose once asthma stability is achieved.

Patients should be instructed to prime PULMICORT TURBUHALER prior to its initial use, and instructed to inhale deeply and forcefully each time the unit is used. Cleaning the mouth after inhalation is also recommended.

**Directions for Use:** Illustrated Patient's Instructions for Use accompany each package of PULMICORT TURBUHALER.

#### NOW SUPPLIED

PULMICORT TURBUHALER consists of a number of assembled plastic parts, the main parts being the dosing mechanism, the storage unit for drug substance and the mouthpiece. The unit is protected by a white outer tube; cover screwed onto the tube. The body of the inhaler is white and the lung grip is brown. The following warning is printed on the grip in raised lettering: "Pulmicort 200" TURBUHALER cannot be refilled and should be discarded when empty.

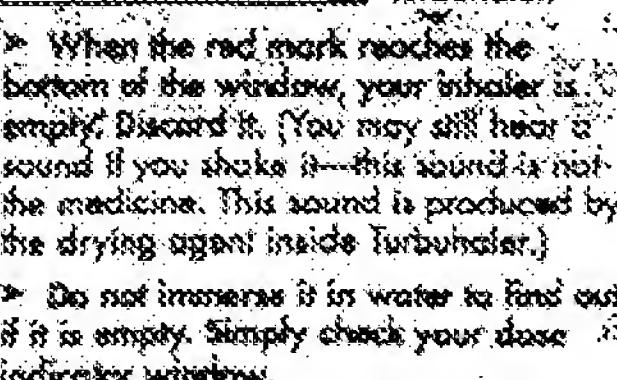
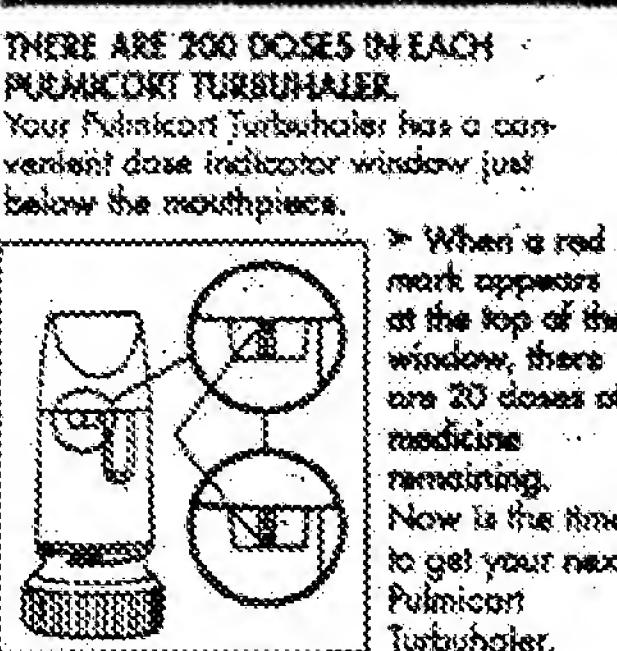
PULMICORT TURBUHALER is available as 200 mcg/dose, 200 doses.

Store at controlled room temperature 68° to 77°F (20° to 25°C) (90% RH 77°F).

#### FURTHER INFORMATION ABOUT PULMICORT TURBUHALER

Pulmicort Turbuhaler delivers your medicine to every lung powder that you may not taste, smell, or feel. By following the instructions for use of this inhaler, you can be confident that you have received the correct dose.

- Pulmicort Turbuhaler should not be used with a spacer.
- Pulmicort Turbuhaler contains only budesonide and does not contain any inactive ingredients.
- Pulmicort Turbuhaler is specially designed to deliver only one dose at a time, no matter how often you click the brown grip. If you accidentally blow into your inhaler after loading a dose, simply follow the instructions for loading a new dose.



When the red mark reaches the bottom of the window, your inhaler is empty. Discard it. You may still hear a sound if you shake it—this sound is not the medicine. This sound is produced by the drying agent inside Turbuhaler.

Do not immerse it in water to find out if it is empty. Simply check your dose indicator window.

This inhaler does not contain the complete information about your medicine. If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If you have further questions about the use of Pulmicort Turbuhaler, call:

1-800-343-4777

or 033-70-0-30-000341800. 6/97

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